REMARKS

A. Interview with the Examiner

Applicants thank Examiner Lakia Tongue and Examiner Vanessa Ford for the courtesy extended to their representatives, Joseph D. Eng Jr. and Kenneth H. Sonnenfeld, during their meeting and interview at the U.S. Patent and Trademark Office on May 24, 2011. During the interview, possible claim amendments were discussed, along with the references that were cited in the pending office action and International Application No. WO 2002/07773 to Waugh et al. (hereafter "Waugh '773").

In addition, Examiner Tongue kindly indicated that, prior to the issuance of the next office action, she would consider a supplemental amendment containing claim amendments consistent with the discussions during the interview. Applicants have taken up the Examiner's offer and hereby submit this supplemental amendment.

B. Explanation of the Amendments

In the claim listing that begins on page 2 of this paper, the claim amendments from Applicants' December 13, 2010 paper are still shown in marked-up format, since these claim amendments have not yet been entered. Accordingly, added language is underlined, and deleted language is indicated either with double brackets or crossed out with a single line.

In this paper, Applicants have amended independent claim 51 to specify that "the botulinum toxin is not covalently modified." Support for this amendment is generally found throughout the specification. For example, support is found in examples 2-5, which describe methods of administering botulinum toxin by topically applying a botulinum toxin without any covalent modification to the skin or epithelium of a subject. Applicants further note that

¶ [0084] of the originally filed specification provides support by explicitly stating that "the peptidyl transdermal carrier can transport a therapeutically effective amount of botulinum therapeutic across skin ***without covalent modification*** of the therapeutic." ¶ [0084] (emphasis added). Paragraph [0096] of the originally filed specification also provides support for this claim language by stating that the botulinum toxin crosses skin "without prior covalent modification." Accordingly, Applicants respectfully submit that no new matter has been added by the introduction of this claim language.

C. Waugh '773 Does Not Anticipate or Render Obvious the Presently Pending Claims

The present claims are directed to "[a] method of administering a botulinum toxin to a subject." See, e.g., claim 51. The method comprises "topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric backbone having attached positively charged efficiency groups." *Id*. In addition, the claims, as amended herein, specify that "the botulinum toxin is not covalently modified."

In the previous paper filed December 13, 2010 ("the December 13th Amendment"), Applicants discussed the Waugh '773 reference. In particular, Applicants noted that while Waugh '773 was not cited by June 11, 2010 Office Action issued for this case, it had been cited during the examination of co-pending U.S. Application No. 11/072,026. In the December 13th Amendment, Applicants addressed the Waugh '773 reference, noting that it does not anticipate any of the claims in the pending case, because Waugh '773 does not disclose "any method of administering botulinum toxin to a subject" in which "the carrier and the botulinum toxin non-covalently and directly associate," as required by the claims.

During the May 24, 2011 interview, Applicants' representatives discussed the Waugh '773 reference with Examiners Tongue and Ford. In particular, Applicants' representatives noted that to the extent that Waugh '773 mentions botulinum toxin, it requires it to be covalently attached to a negatively charged backbone. See, e.g., Waugh '773 at pp. 10 and 15-17. In other words, it requires the botulinum toxin to be covalently modified. The claims of the present case, however, specify that "the botulinum toxin is not covalently modified." Accordingly, Applicants respectfully assert that the present claims are not anticipated by Waugh '773.

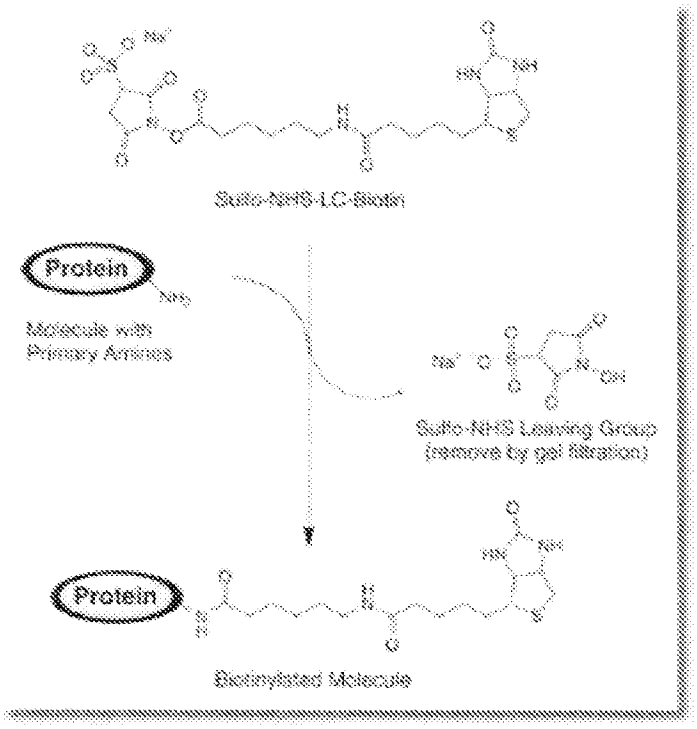
Applicants' representatives further noted during the interview that the Information Disclosure Statement filed on May 20, 2011 included a Written Opinion issued for a European counterpart application of a U.S. Appln No. 11/073,307, a case that is related to the present case. In that Written Opinion, the European Examiner argued that the claims in the European counterpart to U.S. Appln. No. 11/073,307 lacked inventive step over Example 4 of the Waugh.

In the interest of moving prosecution along, Applicants take this opportunity to discuss Example 4 of Waugh '773, even though no rejection has been issued in this case specifically based on Example 4 of Waugh '773. In particular, Applicants respectfully assert that Example 4 of Waugh does not render the presently claimed invention obvious. As noted above, Waugh '773 discloses that proteins, such as botulinum toxin, must be covalently attached to a negatively charged backbone. The negatively charged backbone is used to promote complex formation with a positively charged backbone.

Example 4 of Waugh '773 merely describes a variation of this approach. Example 4 concerns the delivery of biotinylated insulin across skin using a carrier referred to as "KNR," which Waugh '773 describes as polylysine having attached efficiency groups. Unlike some of the other embodiments in Waugh '773, the insulin to be delivered is not covalently attached to a

negatively charged polymeric backbone. Instead, Applicants point out, the insulin is covalently attached to multiple negatively charged biotin molecules.

Specifically, the insulin to be delivered is covalently modified by attaching separate sulfo-NHS-LC groups, as described in the reaction scheme below:



Reaction scheme for Thermo Scientific EZ-Link Sulfo-NHS-Biotin Reagents. This example features the long-chain (LC) version of this class of reagent (Sulfo-NHS-LC-Reagent, Part No. 21335).

See Pierce Protein Research Projects, "EZ-Link Sulfo-NHS-Biotin and Biotinylation Kits," submitted herein in a Supplemental SB08 Form. Example 4 of Waugh '773 discloses that there is a 12-fold molar excess of biotin with respect to insulin, so that there are, on average, twelve biotin molecules attached to each insulin via the mechanism shown above. ***Critically***, one of ordinary skill in the art would have recognized, at the time the invention was filed, that biotin is negatively charged in aqueous solution. See, e.g., Naujoks et al., Colloids and Surfaces A: Physiochem. Eng. Aspects 249 (2004) at page 71, col. 2, last paragraph (describing IgG-biotin

stabilized droplets as carrying a negative charge). See also, George et al., Adv. Mater., (2006) Vol. 18, at p. 577-581 (specifically, see p. 577, col. 2, lines 11-13, describing the earlier study by Naujoks in 2004 as establishing that biotin is negatively charged in aqueous solution). Therefore, on average, each insulin carries about twelve negative charges from the covalently attached biotin.

In other words, Example 4 of Waugh '773 merely shows that a protein can be functionalized by negative charges distributed directly on the protein, as an alternative to attachment to a negatively charged polymeric backbone, as described in the other embodiments of Waugh '773. In any event, in both cases Waugh '773 teaches that a protein must be covalently modified -- either by attaching it to a negative charged backbone or to individual negatively charged groups like biotin -- in order to be able to associate the protein to a positively charged backbone carrier.

By contrast, the presently claimed invention concerns botulinum toxin -- rather than insulin -- and further specifies that "the botulinum toxin is not covalently modified." Accordingly, Applicants respectfully assert that the presently claimed invention is not obvious over Example 4 of Waugh '773.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this response to Deposit Account No. 50-3732, Order No. 13720-105071US2.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-3732, Order No. 13720-105071US2.

Respectfully submitted,
KING & SPALDING, L.L.P.

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By: /Joseph D. Eng Jr./
Joseph D. Eng Jr.
Registration No. 54,084

Correspondence Address:
King & Spalding LLP
1185 Avenue of the Americas
(212) 827 - 4318 Telephone
(212) 556 - 2222 Facsimile